Appointment

From: Katya Tsaioun [Personal Email / Ex. 6]
Sent: 10/18/2017 8:48:46 PM
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Subject: SRA Symposium: Application of Systematic Reviews in Risk Assessment: Case Studies, Successes and Challenges from Different Domains
Location: Crystal Gateway Marriott, 1700 Jefferson Davis Highway, Arlington, Virginia 22202. Room: Salon K

Start: 12/11/2017 3:30:00 PM
End: 12/11/2017 5:00:00 PM
Show Time As: Busy

Recurrence: (none)

Room: salon K

Chair(s): Katya Tsaioun [Personal Email / Ex. 6]

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The public increasingly demands transparent and objective risk assessment of chemicals that are used in their daily lives and are released into the environment. These safety assessments become the scientific foundation of risk analysis and subsequently public policy. In clinical research, the Evidence-based methods (EBM) approaches brought the consistent framework, higher standards, objectivity, consistency and transparency. Systematic reviews (SRs), the principal tool of EBM, are studies that collect and summarize available evidence in a rigorous, transparent and objective manner according to an a priori process described in the protocol. In this session, we will demonstrate that EBM, and SRs could be successfully used for risk assessment. In this session the presenters from diverse fields of public health, industry, academia and regulatory agencies will present case studies where they applied the EBM principles to different problems in hazard identification, and exposure and risk assessment. The theory and principles of evidence-based methodologies will be described, challenges of adopting these methods from clinical medicine to toxicology and risk assessment will be highlighted by speakers from government agencies, academia and industry, and examples of applications of this approach to public health problem, chemicals risk assessment and safety test methods comparison will be described. One of the specific challenges in adapting the SR methods to toxicology and risk assessment is integration of multiple streams of evidence and assessing their quality. A case study on development of a framework for quantitative consideration of study quality and relevance in the evaluation of one data stream will be illustrating a proposed solution. In summary, we argue that EB methods and SRs, when adopted by industry and regulators, can bridge the gap between the scientific evidence and confidence of regulatory decisions, and increase the public understanding of the process.

M2-I.1 10:30 am Introduction to systematic reviews: methods and concepts developed in clinical medicine and their applicability to other domains. *Tsaioun K*; Johns Hopkins Bloomberg School of Public Health* [Personal Email / Ex. 6]

Abstract: Systematic reviews help clinicians keep abreast of the medical literature by summarizing large bodies of evidence and helping to explain differences among studies on the same question. Used to inform medical decision making, plan future research agendas, and establish policy, systematic review methods are ready to be adopted in risk assessment. We will provide a primer on key elements such as review registration, protocol development, systematic databases searches, and meta-analysis. In addition, the concepts of internal validity (i.e. 'risk of bias') and external validity (i.e. generalizability of results) will be discussed. The presentation will conclude with an introduction to a case study on the application of these principles to Tox21 test methods comparison to traditional toxicological methods.

M2-I.2 10:50 am Development and refinement of a framework for quantitative consideration of study quality and relevance in the evaluation of mechanistic data based on Key Characteristics of Carcinogens
. *Wikoff DS*, Rager JE, Harvey S, Haws L, Chappell G, Borghoff S;* Personal Email / Ex. 6

Abstract: Evaluation of mechanistic data in a systematic review is an element unique to the field of toxicology; methods established in evidence-based medicine are not sufficient to integrate this data stream. Smith et al., (2016) described an approach to organize mechanistic data via ten key characteristics of carcinogens (KCC). However, this approach does not incorporate data quality, directionality, and concordance with adverse outcomes – concepts key to use in risk assessment. Thus, a framework that integrates these elements is proposed; it has three components (reliability, strength, and activity) that are evaluated using an algorithm which provides a score for each KCC and subsequently categorization as weak/moderate/strong. Reliability scores provide a measure of study quality. Strength scores provide a measure of relevance for each model, which are used to characterize applicability to the evaluation of carcinogenicity in humans; this component considers both the number of models and assays. Activity scores account for active/inactive results. The algorithm allows for flexibility in component weighting, and the scoring approach allows for the incorporation of many study types, including high throughput screening data. Resulting data are then considered relative to animal and human evidence streams, and tumor responses. Application of this framework to multiple mechanistic datasets for chemicals associated with different types of cancers and in different models demonstrates that simple categorization of data by KCC are not alone sufficient, and that evaluation of complex and diverse data (i.e., endpoints measured at the organ, cellular, and molecular level) relative to tumors observed in other evidence streams is critical. The proposed framework provides a quantitative approach that accommodates data quality and relevance, thus increasing the utility of evaluating and integrating the identified KCC, as well as providing a transparent and reproducible process for assessment of mechanistic data in systematic reviews.

M2-I.3 11:10 am Application of Systematic Review: An Industry Perspective. *Lewis RJ*, Freeman J; ExxonMobil Biomedical Sciences* Personal Email / Ex. 6

Abstract: Systematic review has gained considerable interest in both the regulatory and regulated scientific communities. Adoption of systematic review methods by both regulatory and regulated entities could significantly enhance transparency and reproducibility as well as quality of chemical health risk assessments. However, conducting systematic review is difficult, time consuming and potentially costly. Also, a number of approaches and frameworks have been proposed. Collectively, these issues can confound appropriate use of systematic review. Herein, we will attempt to address some of these issues. This presentation will describe an industry perspective regarding potential benefits and challenges in applying systematic review to chemical health risk evaluation. Examples related to reviews of human studies for environmental exposure to hydrogen sulfide and cancer mortality among refinery workers will be described to illustrate efforts to advance application of systematic review methods in an industrial setting. Challenges in applying systematic review methods will also be described, along with potential research needs to further enhance adoption and use of these methods by the scientific community.

M2-I.4 11:30 am Systematic Review of Factors Affecting the Onset and Progression of Neurological Disease. *Krewski D*; University of Ottawa* Personal Email / Ex. 6

Abstract: As part of the National Population Health Study of Neurological Conditions initiated by the Public Health Agency of Canada in collaboration with the National Health Charities of Canada, systematic reviews of factors associated with the onset and progression of 14 neurological conditions were conducted according to a common core protocol The 14 conditions included: Alzheimer's disease, amyotrophic lateral sclerosis, primary brain tumours, cerebral palsy, dystonia, epilepsy, Huntington's disease, hydrocephalus, multiple sclerosis, muscular dystrophies, neurotrauma, Parkinson's disease, spina bifida, and Tourette's syndrome. The findings of this comprehensive review are summarized both within and across conditions. These results will be of value in developing strategies for mitigating the growing burden of neurological disease both in Canada and internationally.

M2-I.5 11:50 am Challenges in Implementing Systematic Review in TSCA Risk Evaluations. *Camacho-Ramos I*; U.S. Environmental Protection Agency* camacho.iris@epa.gov

Abstract: The amended Toxic Substances Control Act (TSCA) requires EPA to develop fit-for-purpose risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment. The risk evaluation must integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment, and information on potentially exposed or susceptible subpopulations. To meet these requirements, EPA is implementing systematic review across various multi-disciplinary lines of evidence supporting the risk evaluation (i.e., exposure, fate, ecological hazard, and human health hazard). This presentation discusses the challenges of conducting systematic review within the TSCA regulatory framework and explores opportunities geared towards establishing a sustainable systematic review environment under TSCA.